Thrombosis and Drug-Eluting Stents: A Critical Appraisal

Dean J. Kereiakes, MD, FACC, Joseph K. Choo, MD, John J. Young, MD, Thomas M. Broderick, MD

The Lindner Center for Research & Education, Ohio Heart Health Center, Cincinnati, OH

The clinical consequences of stent thrombosis are frequently catastrophic. This article reviews the factors previously implicated in the occurrence of stent thrombosis and analyzes recent reports of thrombosis involving a new sirolimus-eluting stent (Cypher). Factors associated with stent thrombosis include intrinsic stent thrombogenicity and patient-, target lesion-, and procedure-related issues. Stent design may influence the degree of platelet activation after coronary stent deployment. In drug-eluting stents, the mechanical properties of the bare metal stent platform might be altered by the polymer coating, and the propensity for thrombosis might be influenced by both the polymer coating and the medication with which it is impregnated. Cumulative data for the Cypher stent do not suggest a propensity for thrombosis, but several caveats should be observed to enhance the safety of the device.

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Key words: Stents • Thrombosis • Sirolimus • Paclitaxel • Heparin

Thrombotic occlusion of metallic coronary stent prostheses has been a concern since the introduction of coronary stenting in 1986.[1] Numerous and diverse factors have been associated with stent thrombosis (Figure 1) and include intrinsic stent thrombogenicity and patient-, target lesion-, and procedure-related issues.[2] The U.S. Food and Drug Administration's approval and release of the Cypher sirolimus-eluting stent (Cordis Corporation, Miami Lakes, FL) represents a potential landmark event for percutaneous vascular intervention.

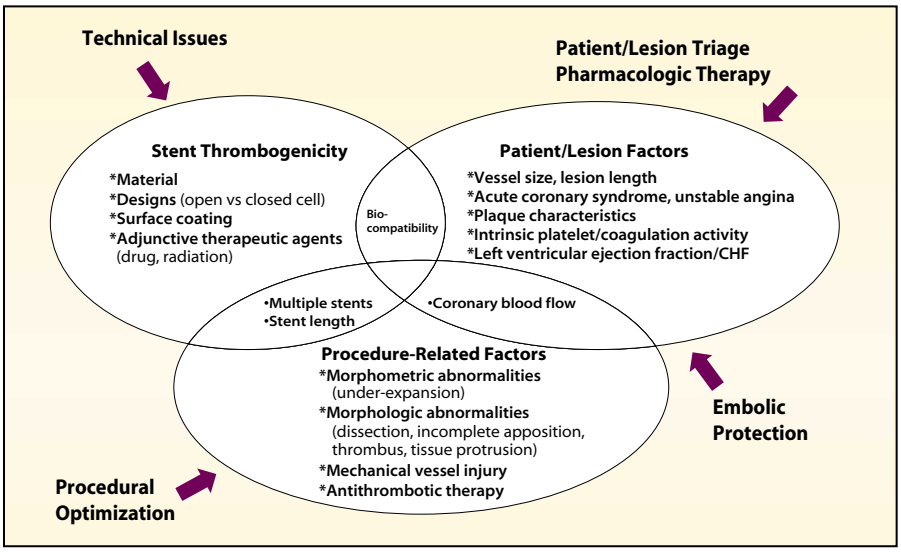


Figure 1. *Multiple and diverse factors contributing to stent thrombosis. CHF, congestive heart failure. Modified with permission from Honda and Fitzgerald.[2]*

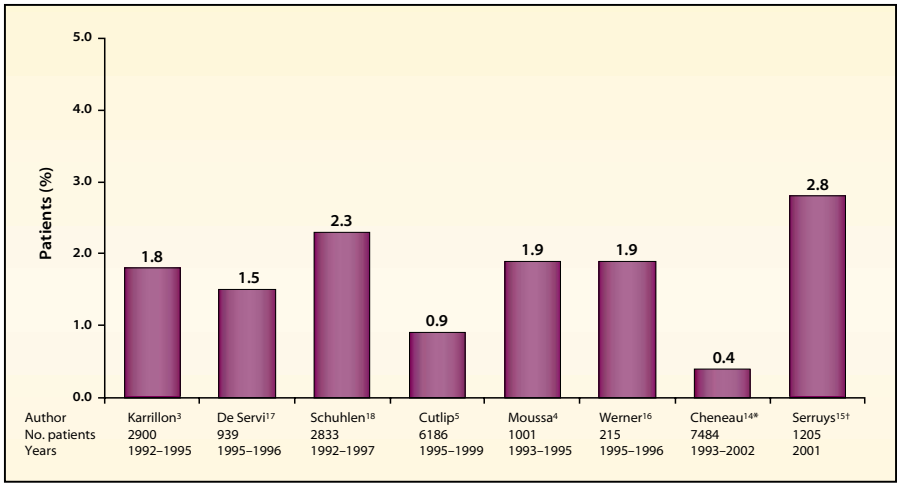
Although marked reductions in restenosis and repeat revascularization rates have been observed with Cypher (vs bare metal Bx Velocity stent [Cordis]) in randomized trials, problems with limited availability of the Cypher stent have arisen, as have economic and, more recently, safety concerns. Indeed, news media coverage has heightened the public's awareness of concern over the potential thrombogenicity of this new device. It is appropriate at this time to review the factors previously implicated in the occurrence of stent thrombosis and to analyze recent reports of thrombosis involving new drug-eluting stent prostheses.

The Problem

Stent thrombosis might be related to intrinsic thrombogenicity of the specific alloy or materials used in stent construction. Stent design (ie, open vs closed cell), surface coating, and the addition of adjunctive pharmacotherapeutic agents might influence the degree of platelet activation or propensity for thrombus development. Deployment of multiple stents, as well as stent length, might also contribute to the risk for stent thrombosis. Similarly, patient- and arterial lesion–related factors, including the presence of an acute coronary syndrome, intrinsic platelet or coagulation activity, smaller vessel caliber, longer lesion length, presence of thrombus, and depressed left ventricular ejection fraction, have all been associated with stent thrombosis.[3–7] In addition, suboptimal stent deployment (ie, under-expansion, incomplete apposition) and type and duration of periprocedural/postprocedural adjunctive antithrombotic therapy are important contributing factors.[8–11] Despite optimized techniques of high-pressure deployment with intravascular ultrasound (IVUS) guidance and postprocedural combination antiplatelet therapy, stent thrombosis has not been eliminated in the "modern" stent era.

The clinical consequences of stent thrombosis are frequently catastrophic and include death in 20% to 48% or major myocardial infarction in 60% to 70% of persons who experience this event.[3–5,12,13] The recorded incidence of stent thrombosis in the modern era of stent deployment varies from a low of 0.4% with IVUS guidance[14] to a high of 2.8% after multivessel stenting[15] (Figure 2). Although both the definition and mechanism for detection vary between reported series, stent thrombosis has been reported to complicate coronary stent deployment in 1.2% of 22,763 patients.[3–5,14–18] Finally, stent thrombosis is associated with significant economic impact. A recent retrospective analysis identified median hospital costs exceeding

Figure 2. *Stent thrombosis after deployment of bare metal stents. Experience from eight clinical series in 22,763 patients. *Intravascular ultrasound (IVUS) guided. †Multivessel stenting per patient. Adapted from Honda and Fitzgerald.[2]*



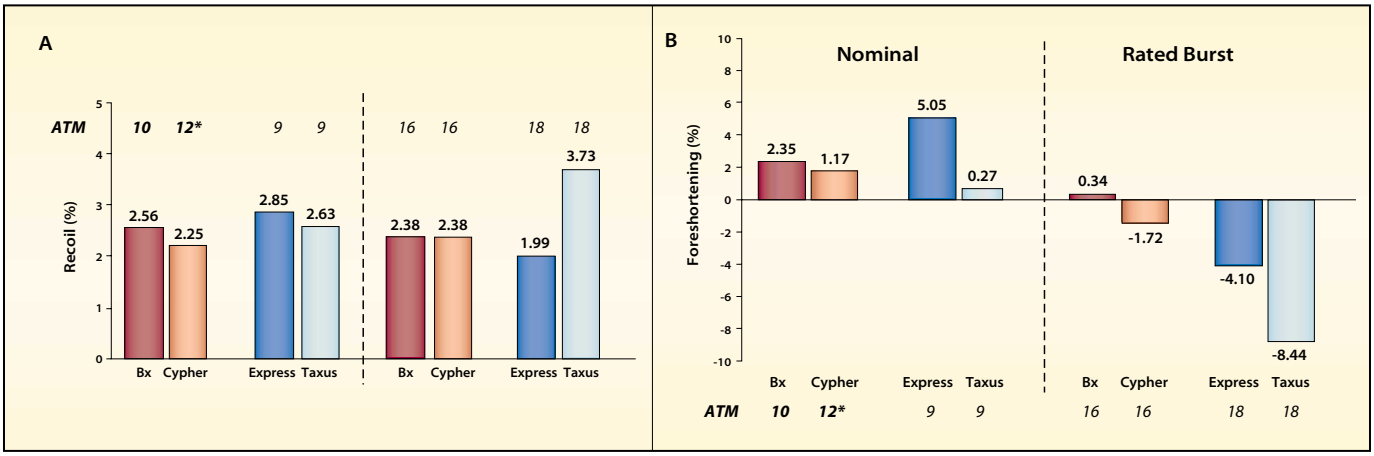


Figure 3. (A) *In-vitro testing of stent recoil at nominal and rated burst pressures in Bx Velocity (Bx), Cypher, Express, and Taxus stents. Note that nominal pressure for the Cypher stent is 12 atm and for the Bx stent is 10 atm.* **(B)** *In-vitro testing of stent foreshortening at nominal and rated burst pressures in the four stents. *Nominal pressure difference due to variation in "crimp and load" process. Data provided by Randy Grishaber, Senior Engineer, Advanced Research and Development, Cordis Corporation.*

$11,000 per stent thrombosis event.[19]

Drug-Eluting Stents

On July 7, 2003, a "Dear Colleague" letter was circulated to interventional cardiologists by Cordis Corporation that detailed isolated cases of Cypher stent thrombosis, as well as potential contributory factors. The public news media immediately sensationalized components of this letter, raising public and professional concerns that the Cypher stent might be associated with an increased incidence of thrombosis. It is both timely and pertinent to evaluate what data are available on the Bx Velocity (Bx) stent platform, polymer coating, sirolimus, and other factors that might or might not contribute to thrombogenicity.

The media immediately sensationalized components of this letter, raising concerns that the Cypher stent might be associated with an increased incidence of thrombosis.

First, stent design might influence the degree of platelet activation after coronary stent deployment.[20] In a randomized trial, an open-cell stent design (vs closed-cell design) was associated with a greater degree of platelet activation at 24 hours and 30 days.[21] Interestingly, the Bx stent has a closed-cell design and should be associated with a lesser degree of platelet activation. It might be, however, that basic stent platform performance characteristics are altered when the stent is coated with a nonresorbable polymer and drug. Mechanical testing and comparison of the basic stent platform with its drug-eluting version might provide insight into this question.

An in-vitro comparison of the Bx and Cypher stents demonstrates that nominal deployment pressure is 2 atm higher for Cypher (12 atm vs 10 atm for Bx). This appreciable difference in nominal deployment pressure has been ascribed to variation in the "crimp and load" process for securing the stent on the delivery balloon system rather than to intrinsic differences in the stent device itself. Nevertheless, operators who are not cognizant of this fact will systematically under-deploy the Cypher stent if nominal deployment pressure for the Bx is used. The in-vitro comparison of stent recoil and foreshortening at both nominal and rated burst pressures (Figure 3) demonstrates little difference between the Bx and Cypher stents. Conversely, the elastomeric properties of the polymer used to coat the Express 2 stent (Boston Scientific, Natick, MA) during production of the paclitaxel-eluting Taxus stent (Boston Scientific) are evident. The Taxus and Express are both nominal at a similar, and lower (9 atm) pressure than either the Bx or Cypher stents. At rated burst pressure (18 atm), the Taxus demonstrates a degree of recoil and foreshorten-

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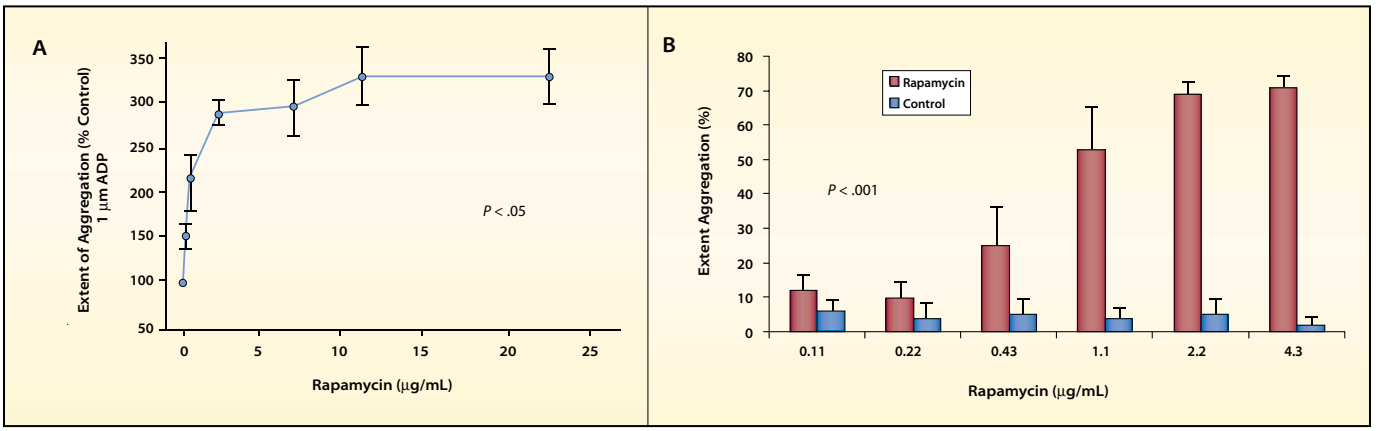


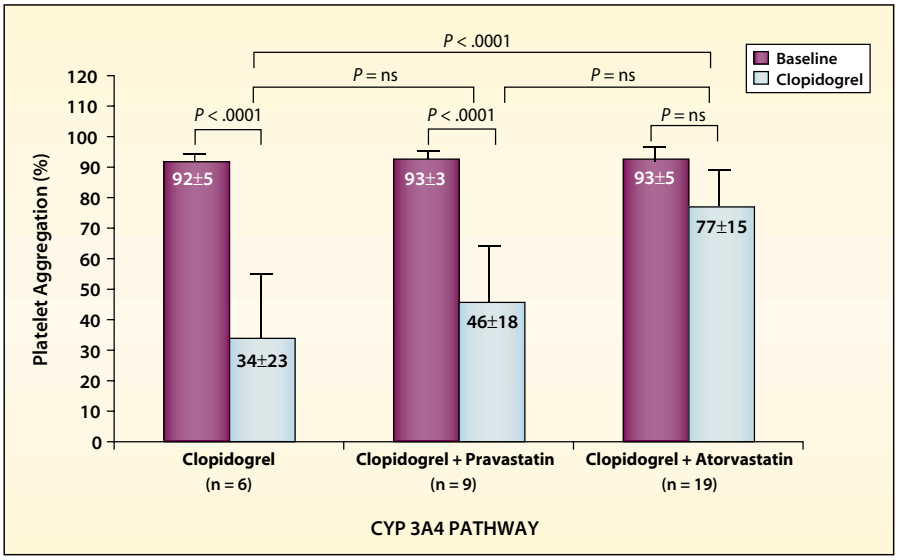
Figure 4. (A) *Dose–response enhancement of platelet aggregation by incremental concentrations of rapamycin during in vitro testing.* **(B)** *Enhancement of thrombin receptor-activating peptide–induced platelet aggregation by incremental concentrations of rapamycin during in vitro testing. Reproduced with permission from Babinska et al.*[22]

ing twice that of the Express. Because the stent devices are similar, the observed differences must reflect the properties of the polymer. The point to be made, which is applicable to all drug-eluting stent devices, is that the mechanical properties of the bare metal stent platform might be altered by the polymer coating.

Furthermore, the propensity for thrombosis might be influenced by both the polymer coating and the medication with which it is impregnated. For example, sirolimus (rapamycin) has been demonstrated to enhance platelet aggregation in response to low levels of agonists (adenosine diphosphate or thrombin receptor-activating peptide).[22] A systemic concentration of 1.1 μg/mL rapamycin can be obtained after deployment of two Cypher stents[23] and is associated with markedly enhanced platelet aggregation (Figure 4). Local concentrations of rapamycin at the site of stent deployment should far exceed those evaluated in these in vitro analyses. In addition, rapamycin is metabolized via the hepatic CYP 3A4 P-450 enzyme system, similar to clopidogrel, atorvastatin, diltiazem, and antifungal agents.[23] It has been proposed that agents that use this pathway (such as atorvastatin) might interfere with hepatic conversion of clopidogrel (a prodrug) to its active moiety and thus might diminish clopidogrel-induced platelet inhibition[24] (Figure 5). This type of drug–drug interaction could be of greater significance to individuals with genetically determined diminished CYP 3A4 activity who manifest a reduced response to clopidogrel platelet inhibition[25] (Figure 6).

Finally, problems with optimal Cypher stent deployment have been compounded by marked limitations in Cypher stent availability, which have resulted in severe shortages of many stent sizes. Many physicians have resorted to deploying much longer stents than are required or to using smaller-diameter stents and postdilating them with larger bal-

Figure 5. *Ex vivo platelet aggregation at baseline and after clopidogrel administration in separate cohorts of patients by type of statin therapy (pravastatin vs atorvastatin vs none). Patients who received atorvastatin in this study manifested a diminished level of platelet inhibition in response to clopidogrel therapy. Atorvastatin (vs pravastatin) is metabolized by the hepatic CYP 3A4 cytokine P450 system, which also converts clopidogrel (a prodrug) to its active moiety. Reproduced with permission from Lau et al.*[24]



loons. This phenomenon of choosing the "wrong stent for the job" by default has no doubt exacerbated the likelihood of suboptimal stent deployment and, thus, thrombosis.

Cypher Thrombosis

The cumulative clinical experience to date with both Hepacoat[26–30] (Cordis) and Cypher stents[31–33] (personal communication, Erick Schampaert, MD, March 29, 2003) is summarized in Figure 7. The Hepacoat stent is a heparin-coated Bx stent that has been evaluated in three randomized trials and in nonrandomized registries. In the randomized trial experience with Hepacoat,[26–28] a stent thrombosis rate of 0.40% was observed (0.70% in patients treated for acute myocardial infarction and 0.10% for elective procedures). The registry experience with Hepacoat has similarly suggested a low incidence (0.15%–0.50%) of stent thrombosis. The Cypher stent has been evaluated in four randomized trials in comparison with the Bx stent[31–33] (personal communication, Erick Schampaert, MD, March 29, 2003). The aggregate of randomized trial data suggest a low (0.60%) rate of Cypher thrombosis, which is comparable to the cumulative experience in two "real-world" registries of Cypher stent deployment (0.80%).[34,35] The most recently updated postmarket surveillance of Cypher stenting in practice (the "e-Cypher" registry) demonstrates a stent thrombosis rate of 0.87% (personal communication, Philip Urban, MD, September 15, 2003). This experience must be viewed in the context that 95% of these patients received combination oral antiplatelet therapy for at least 2 months and more than 60% for at least 3 months after Cypher stent deployment. A very recent experience describes intraprocedural stent thrombosis in five of 670 consecutive patients treated with the Cypher stent (Antonio Columbo, MD, personal communication, November 11, 2003). Multivariate analysis identified maximum stent length per vessel and lack of adjunctive platelet glycoprotein IIb/IIIa inhibition as independent correlates of intraprocedural thrombosis. Intraprocedural thrombosis is a distinctly unusual complication of bare metal stent deployment and is usually associated with acute myocardial infarction, thrombus-containing lesions, or residual intimal dissection. Thus, the overall clinical experience to date with

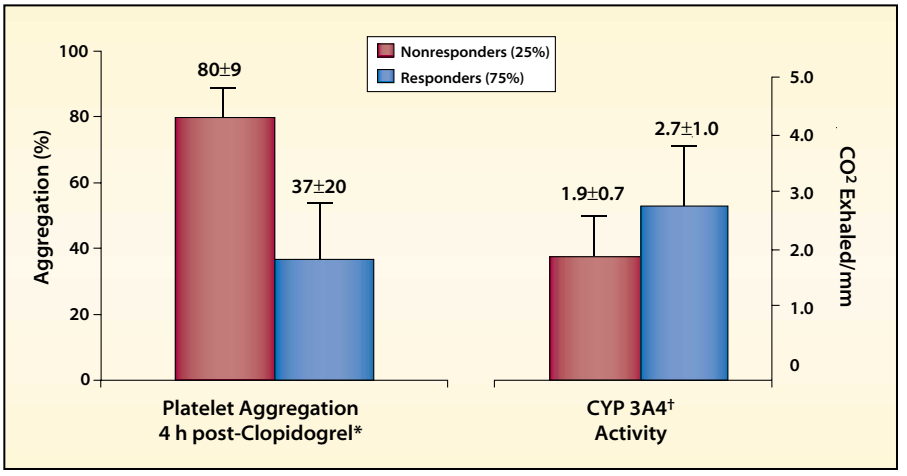
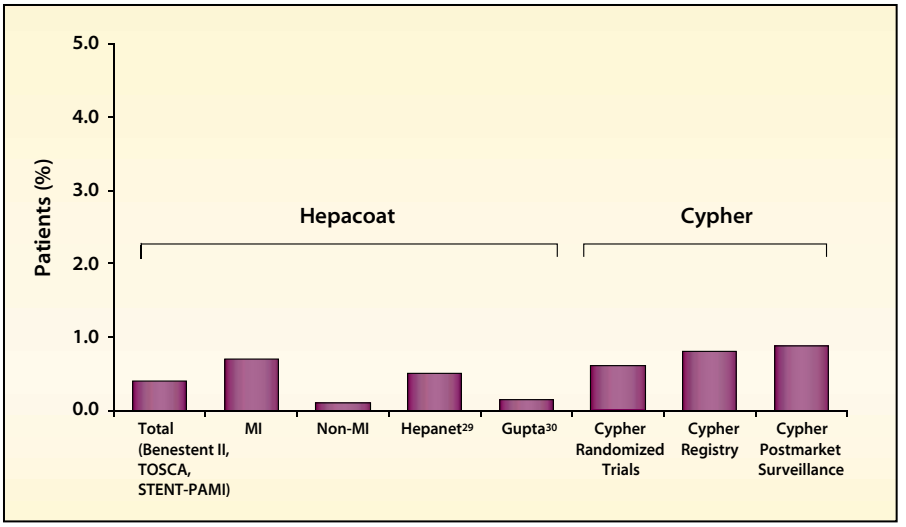


Figure 6. *Ex vivo platelet aggregation at baseline and 4 hours after a clopidogrel (450-mg) oral loading dose. One fourth of patients manifest a diminished platelet inhibitory response to clopidogrel. Diminished clopidogrel response was correlated with diminished CYP 3A4 enzyme activity, as reflected in the results (CO^2 exhaled) of erythromycin breath testing. *450 mg p.o. (P = .0002). †P = .15. Adapted from Lau et al.[25]*

Figure 7. *Stent thrombosis in the clinical experience with Hepacoat and Cypher stents. In three randomized clinical trials of the Hepacoat stent (Benestent II,26 TOSCA,27 STENT-PAMI28), the incidence of stent thrombosis was 0.40% overall (0.70% in patients treated for acute myocardial infarction [MI] and 0.10% in patients who underwent elective stent deployment). Hepanet is an Internet-based registry for the clinical experience with the Hepacoat stent. In randomized trials of the Cypher stent (SIRIUS,31 C-SIRIUS [personal communication, Erick Schampaert, MD, March 29, 2003], E-SIRIUS,32 RAVEL33) and in the combined single-center registries (Research34 and Milan35), the incidence of stent thrombosis is shown. Cypher postmarket surveillance comprises the e-Cypher Internet-based clinical registry (personal communication, Philip Uban, MD, September 15, 2003).*



the Cypher stent does not suggest an increased propensity for stent thrombosis.

Summary and Recommendations

Although the cumulative data for the Cypher stent do not suggest a propensity for thrombosis, several caveats regarding device safety must be mentioned. First, the nominal deployment pressure for the Cypher stent exceeds the Bx by 2 atm, and higher pressures must be used to ensure optimal deployment. Second, it is better to optimally deploy the appropriately sized bare metal stent than to deploy a Cypher stent that is too long or too small. Third, the low rates of Cypher stent thrombosis observed in clinical trials and the e-Cypher postmarket surveillance must be viewed in the context of extrapolation of the results of clinical trials to different periprocedural adjunctive pharmacologic treatment regimens might not be sound.

Table 1
Cypher Thrombosis Recommendations

- Optimize stent size (length and diameter)
- Optimize stent deployment (pre- and postdilate; higher pressures; IVUS)
- Optimize adjunctive pharmacology to conform with clinical trials and labeling
  - Procedure: UFH, GP IIb/IIIa inhibitors (complex/multiple stent)
  - Postprocedure: extend combination antiplatelet therapy at least 2–3 months

UFH, unfractionated heparin; GP, glycoprotein.

Multivariate analysis identified maximum stent length per vessel and lack of adjunctive platelet glycoprotein IIb/IIIa inhibition as independent correlates of intraprocedural thrombosis.

at least 2 to 3 months of combination oral antiplatelet therapy. Early (< 2 months) discontinuation of combined antiplatelet therapy might be associated with an increased likelihood of thrombosis. Similarly,

Finally, the following recommendations can be made (Table 1). Every effort should be made to optimize stent size (both length and diameter) and deployment. Care should be taken to predilate the target stenosis. Postdilatation with high-pressure inflation (≥ 14 atm) should be performed, and IVUS can be used to ensure optimal deployment if questions remain. Periprocedural glycoprotein IIb/IIIa inhibitors should be used for complex stent procedures, long stents, and/or procedures that require multiple Cypher stents. Adjunctive GP IIb/IIIa inhibition might be desirable, owing to both

Main Points

- The recorded incidence of stent thrombosis in the modern era of stent deployment varies from a low of 0.4% with intravascular ultrasound guidance to a high of 2.8% after multivessel stenting.
- Numerous and diverse factors have been associated with stent thrombosis and include intrinsic stent thrombogenicity and patient-, target lesion-, and procedure-related issues.
- In all drug-eluting stent devices, the mechanical properties of the bare metal stent platform might be altered by the polymer coating, and the propensity for thrombosis might be influenced by both the polymer coating and the medication with which it is impregnated.
- An in vitro comparison of the Bx and Cypher stents demonstrates that nominal deployment pressure is 2 atm higher for Cypher; operators who are not cognizant of this fact will under-deploy the Cypher stent if nominal deployment pressure for the Bx is used.
- The overall clinical experience to date with the Cypher stent does not suggest an increased propensity for stent thrombosis.
- Periprocedural glycoprotein IIb/IIIa inhibitors should be used for complex stent procedures, long stents, and/or procedures that require multiple Cypher stents.
- Combination postprocedural oral antiplatelet therapy should be extended for a minimum of 2 to 3 months and preferably for at least 1 year.

rapamycin-associated enhancement of platelet aggregation and the potential for CYP 3A4 pathway–mediated interference with clopidogrel platelet inhibition. Last, combination post-procedural oral antiplatelet therapy should be extended for a minimum of 2 to 3 months and preferably, on the basis of recent trial data from non–drug-eluting stents, for at least 1 year. ■

References

1. Sigwart U, Puel J, Mirlovitch V, et al. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. *N Engl J Med*. 1987;316:701–706.
2. Honda Y, Fitzgerald PJ. Stent thrombosis—an issue revisited in a changing world. *Circulation*. 2003;108:2–5.
3. Karrillon GJ, Morice MC, Benveniste E, et al. Intracoronary stent implantation without ultrasound guidance and with replacement of conventional anticoagulation by antiplatelet therapy: 30-day clinical outcome of the French Multicenter Registry. *Circulation*. 1996;94:1519–1527.
4. Moussa I, Di Mario C, Reimers B, et al. Subacute stent thrombosis in the era of intravascular ultrasound-guided coronary stenting without anticoagulation: frequency, predictors and clinical outcome. *J Am Coll Cardiol*. 1997;29:6–12.
5. Cutlip DE, Baim DS, Ho KK, et al. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. *Circulation*. 2001;103:1967–1971.
6. Neumann FJ, Gawaz M, Ott I, et al. Prospective evaluation of hemostatic predictors of subacute stent thrombosis after coronary Palmaz-Schatz stenting. *J Am Coll Cardiol*. 1996;27:15–21.
7. Kabbani SS, Watkins MW, Ashikaga T, et al. Usefulness of platelet reactivity before percutaneous coronary intervention in determining cardiac risk one year later. *Am J Cardiol*. 2003;91:876–878.
8. Urban P, Macaya C, Rupprecht HJ, et al. Randomized evaluation of anticoagulation versus antiplatelet therapy after coronary stent implantation in high-risk patients: the Multicenter Aspirin and Ticlopidine Trial after Intracoronary Stenting (MATTIS). *Circulation*. 1998;98:2126–2132.
9. Schomig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med*. 1996; 334:1084–1089.
10. Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study investigators. *N Engl J Med*. 1998;339:1665–1671.
11. Bertrand ME, Legrand V, Boland J, et al. Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting. The Full Anticoagulation versus Aspirin and Ticlopidine (FANTASTIC) study. *Circulation*. 1998;98:1597–1603.
12. Hasdai D, Garratt KN, Holmes DR Jr, et al. Coronary angioplasty and intracoronary thrombolysis are of limited efficacy in resolving early intracoronary stent thrombosis. *J Am Coll Cardiol*. 1996;28:361–367.
13. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study investigators. *N Engl J Med*. 1994;331:496–501.
14. Cheneau E, Leborgne L, Mintz GS, et al. Predictors of subacute stent thrombosis: results of a systemic intravascular ultrasound study. *Circulation*. 2003;108:43–47.
15. Serruys PW, Unger F, Sousa JE. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease [comment]. *N Engl J Med*. 2001:344:1117–1124.
16. Werner GS, Gastmann O, Ferrari M, et al. Risk factors for acute and subacute stent thrombosis after high-pressure stent implantation: a study by intracoronary ultrasound. *Am Heart J*. 1998;135:300–309.
17. De Servi S, Repetto S, Klugmann S, et al. Stent thrombosis: incidence and related factors in the RISE Registry (Registro Impianto Stent Endocoronarico). *Catheter Cardiovasc Interv*. 1999;46:13–18.
18. Schuhlen H, Kastrati A, Dirschinger J, et al. Intracoronary stenting and risk for major adverse cardiac events during the first month. *Circulation*. 1998;98:104–111.
19. Reynolds MR, Rinaldi MJ, Pinto DS, et al. Current clinical characteristics and economic impact of subacute stent thrombosis. *J Invas Cardiol*. 2002;14:364–368.
20. Rogers C, Edelman ER. Endovascular stent design dictates experimental restenosis and thrombosis. *Circulation*. 1995;91:2995–3001.
21. Gurbel PA, Callahan KP, Malinin AI, et al. Could stent design affect platelet activation? Results of the Platelet Activation in STenting (PAST) study. *J Invas Cardiol*. 2002;14:584–589.
22. Babinska A, Markell MS, Salifu MO, et al. Enhancement of human platelet aggregation and secretion induced by rapamycin. *Nephrol Dial Transplant*. 1998;13:1353–1359.
23. U.S. Food and Drug Administration, Center for Devices and Radiological Health. Cypher Sirolimus-eluting coronary stent on RAPTOR over-the-wire delivery system or RAPTORRAIL rapid exchange delivery system. Available at: http://www.fda.gov/cdrh/pdf3/p020026.html. Accessed May 27, 2003.
24. Lau WC, Waskell LA, Watkins PB, et al. Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation: a new drug–drug interaction. *Circulation*. 2003;107:32–37.
25. Lau WC, Neer CJ, Watkins PB, et al. Clopidogrel nonresponders discovered during point-of-care platelet aggregation testing [abstract]. *J Am Coll Cardiol*. 2003;41:225A.
26. Serruys PW, van Hout B, Bonnier H, et al. Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). *Lancet*. 1998;352:673–681.
27. Buller CE, Dzavik V, Carerc RG, et al. Primary stenting versus balloon angioplasty in occluded coronary arteries: the Total Occlusion Study of CAnada (TOSCA). *Circulation*. 1999; 100:236–421.
28. Grines CL, Cox DA, Stone GW, et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction. Stent Primary in Acute Myocardial Infarction Study Group. *N Engl J Med*. 1999;341:1949–1956.
29. Mehran R, Lotan C, Kranjec I, et al. The HEP NET study: an Internet-based registry examining efficacy of heparin coating in patients undergoing coronary stent implantation [abstract]. *J Am Coll Cardiol*. 2002;39:75A.
30. Gupta V, Fischell TA, Aravamuthan BR, et al. Use of heparin-coated stents to reduce subacute stent thrombosis: outcome in "real-world" patients. *Am J Cardiol*. 2002;90(suppl 6A):7H.
31. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med*. 2003;349:1315–1323.
32. Schofer J, Schluter M, Gershlick AH, et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E–SIRIUS). *Lancet*. 2003;362:1093–1099.
33. Morice M-C, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med*. 2002;346:2773–2780.
34. Lemos PA, Lee C, Tanabe K, et al. Subacute stent thrombosis after sirolimus-eluting stent implantation in daily practice: results from the Rapamycin Eluting-Stent Evaluated at Rotterdam Hospital (Research) Registry [abstract]. *J Am Coll Cardiol*. 2003;41:23A.
35. Spanos V, Stankovic G, Airoldi F, et al. Use of the sirolimus drug-eluting stent for real world coronary lesions, the Milan experience: results of the first 400 lesions [abstract]. *J Am Coll Cardiol*. 2003;41:13A.